REMARKS

Applicants have received and reviewed the Office Action dated January 23, 2009. By way of response, Applicants have cancelled claim 11 without prejudice and amended claims 1-3 7, 9, 14, 15, 19, 21, 25, 27 and 29-30. No new matter has been added. Claims 1-4, 6-9, 14-19, 21-25 and 27-31 are pending. Applicants submit that the amended claims are supported by the specification as filed.

Support for the recitation in claim 2 of "24 hours" can be found throughout the specification as filed including at least at page 22, line 8. Further support for this recitation is found in the understanding of one skilled in the art of the term "prolonged."

In particular, the amendment to claim 27 is supported in the specification as file at least at page 11, line 4, which states, "The pharmaceutical composition according to this illustrative embodiment further contains at least one second layer, which is referred to as controlled release layer that includes one or more pharmaceutical active agent for controlled delivery, one or more solubilizers, one or more biocompatible swelling agent and a swelling enhancer." Support is also found at page 6, line 14, which states "...and at least one additional layer having one or more active ingredients for controlled drug delivery, one or more solubilizers, one or more biocompatible swelling agents and a swelling enhancer."

For the reasons given below, Applicant submits that the amended claims are in condition for allowance and notification to that effect is earnestly solicited.

Objection to the Specification

The Examiner objected to instances of trademarks appearing in the text of the application as filed. Applicants have amended the specification to capitalize the trademarks, to add the appropriate trademark symbol, and to add generic language where it is useful and does not introduce new matter. The accompanying amended specification refers to the trademarks listed by the Examiner in the manner suggested by the Examiner.

Objection to Claims

The Examiner objected to claims 3, 21 and 29 for minor informalities. The spelling of the words pointed out by the Examiner has been revised or corrected as suggested by the

Examiner. Applicants respectfully submit that the use of "s" ("pregelatinised") where an American would use "z" and the spelling of "labour" are, according to Merriam Webster's Collegiate Dictionary, "chiefly British" spellings that are also acceptable in American English. Nonetheless, Applicants have changed the spellings as suggested by the Examiner.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 1, 2, 7, 9, 11, 15-19, 21, 24, 25 and 30 under 35 U.S.C. § 112, second paragraph. The Examiner objected to certain terms and phrases employed in the claims. Applicants respectfully traverse this rejection.

The Office Action objected to the phrase "low bioavailability", which is employed in claim 1. Applicants respectfully submit that "low bioavailability", implies an absolute bioavailability of less than 60% based on comparison of the bioavailability of active, estimated as area under the curve, on oral administration with that produced upon intravenous administration. This is general description and is known to persons skilled in the art. Accordingly, this phrase is suitable for use in claim 1.

The Office Action objected to the phrases "sufficiently increased" and "prolonged time period" in claim 2. Claim 2 has been amended to include the include "sufficiently increased to not pass through the pyrolus". This puts the phrase "sufficiently increased" in the context of the size of the increase. The term prolonged has been defined by adding time period of up to 24 hours.

Amended claims 7 and 9 employ traditional Markush language, as suggested by the Examiner.

The amended claims no longer recite "preferably", which was objected to in the Office Action.

The Office Action asserted that the recitation of "hydrophilic polymer" in claim 15 lacked antecedent basis. Claim 15 has been amended to recite that "the biocompatible swelling agent is one or more hydrophilic polymers", providing proper antecedent basis.

Claims 19, 24, 25, and 30 have been amended to recite "about" before each number, as is done in the specification as filed.

Claim 21 no longer recites "Amberlite", which was objected to in the Office Action.

Accordingly, Applicants respectfully submit that the amended claims fully comply with § 112, second paragraph, and withdrawal of this rejection is earnestly solicited.

Rejection of Claims Under 35 U.S.C. § 102(b)

The Singh et al. Reference

The Examiner rejected claims 1, 3, 6-9, 11, 14-18, 21 and 24 under 35 U.S.C. 102(b) as being anticipated by Singh et al., WO 2001/022791. Applicants respectfully traverse this rejection.

Amended claim 1 includes the recitation of claim 11, the "ratio of solubilizer to drug of about 1:20 to about 20:1". The Office Action asserts that the Singh et al. reference discloses this ratio. However, the Office Action apparently includes a mathematical error in comparing the ratio in Singh et al. to the ratio recited in the claims. The Office Action states that 0.01 is greater than 0.05 (last full sentence on page 8). In fact, 0.05 is greater than 0.01. Accordingly, the Singh et al. reference does not disclose the presently claimed ratio.

Further, in view of this objection of anticipation, Applicants respectfully submit that, the patent application WO2001/022791 (hereinafter referred to as D1), refers to controlled release compositions of nimesulide comprising nimesulide from 5% to 95% w/w, one or more sustaining materials from 2% to 95% w/w and pharmaceutical excipients from 0% to 90% w/w of the composition, formulated into a controlled release once-a-day dosage form. Singh et al, via D1 provide once-a-day dosage form for nimesulide to improve the possible non-compliance associated with the existing twice daily regimen.

D1 aims to provide once a day compositions of nimesulide but it does not emphasize upon increasing or enhancing its bioavailability. Though D1 discloses compositions of nimesulide, a low solubility, BCS Class II drug, it does not disclose any special efforts to enhance the solubilization of such an active in gastrointestinal fluids with the use of solubilizers for improving or enhancing the bioavailability. D1 just briefly mentions that release modifiers such as solubilizers, pore-formers, pH modifiers amongst others may be incorporated in its formulations. D1, in fact, mainly attempts to provide controlled release nimesulide formulations with reproducible bioavailability by using the active in a micronized form. Use of a drug in a micronized form wherein the particle size of the active has been reduced, is said to only increase the rate of dissolution without increasing the actual solubility of the drug in environment of use,

which is possible with use of instant invention, thereby increasing bioavailability. The use of such a form of the drug in D1 thus does not present a mandatory requirement of solubilizing the drug with the use of solubilizers and is therefore not an object of D1.

In contrast, the present invention focuses upon developing controlled release formulations with improved bioavailability and is based on two integral components: (1) Solubilization of the drug and (2) Gastro-retention of the drug. Herein the low solubility drug is solubilized using solubilizers and the solubilized drug is then incorporated in a gastro-retentive matrix system which remains in the stomach by virtue of its size after swelling and allows a slow and continuous release of the solubilized drug at or near the site of absorption i.e. absorption window which helps in increasing the extent of drug absorption and improving bioavailability.

According to the present invention, increase in solubility of the drug is achieved by using one or more solubilizers. The ratio of solubilizer to drug is about 20:1 to about 1:20. The selection of ratio, as per the present invention depends upon the properties of the active ingredient, the desired improvement in its solubility and the type of solubilizers employed.

This ratio of solubilizer to drug in example 8 of D1 of 2.0/200 = 0.01 falls outside the scope of the range 1/20 = 0.05 to 20/1 = 20 claimed in the present invention. This can be said to be mainly because of the fact that solubilization of the drug with the aid of solubilizers is not within the purview of D1, but D1 focuses upon use of nimesulide in a micronized form for providing compositions with reproducible bioavailability.

Further, with example 5 of D1, again as has been true with example 8 of D1, the ratio of solubilizer to drug employed in example 5 of D1 of 0.7/200 = 0.0035 falls outside the scope of the range claimed by the applicants of the present invention and probably is due to the same reasons as stated above. D1 thereby does not anticipate the present invention.

Hence in view of D1, to overcome the objections raised by the examiner, claim 1 of the present invention has been amended, to include the limitation of ratio of solubilizer to drug of about 1:20 to about 20:1.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the cited reference neither teaches nor suggests the presently claimed compositions, and withdrawal of this rejection is earnestly solicited.

The Doshi et al. Reference

The Examiner rejected claims 27-30 under 35 U.S.C. 102(b) as being anticipated by Doshi et al., US 7,157,100 (prior publication US 2003/0232081). Applicants respectfully traverse this rejection.

Amended claim 27 now recites "a second layer having at least one active pharmaceutical ingredient with a sustained release property, one or more solubilizers, one or more biocompatible swelling agents and a swelling enhancer". Applicants respectfully submit that the Doshi et al. reference does not disclose a composition including such a second layer.

Further, in view of this objection of anticipation raised with respect to Doshi et al (US7157100 B2, prior publication as US 2003/0232081 A1) (hereinafter referred to as D2), the applicants respectfully submit that D2, provides a solid pharmaceutical composition for oral administration containing two or more layers in the form of floating controlled release system for delivery of one or more active agents. The composition of D2 is applicable to drugs exhibiting a "small absorption window" in gastrointestinal tract or to drugs meant to exert localized action in the gastric region; wherein retention of such drugs in the stomach for an extended period of time are said to maximize their absorption. Compositions of D2 comprise a) at least one layer containing active agent and disintegrating agent intended for immediate delivery, b) at least one second layer that includes an active agent for controlled delivery, gas generating component, a matrix forming gelling agent which is intended for controlled delivery of active agent to maintain therapeutic effective concentrations with once a day administration in human body, c) an optional third layer placed between the above two layers comprising an inert excipients, to physically separate the other two layers.

The composition of D2, as disclosed via example 1 is a floating bilayer gastro-retentive system, wherein the second layer swells and gels in the presence of fluid of the gastric environment resulting in volume expansion and entrapping of the gas generated by reaction of gas generating component and the fluid of the environment. The compositions of D2 thus rely on swelling plus gas generation for imparting buoyancy to the dosage form, unlike compositions of the present invention that mainly depend on swelling using a combination of biocompatible swelling agent and a swelling enhancer to achieve gastro-retention. Dosage forms of D2 may therefore require special manufacturing conditions & packs to prevent gas generating reaction

from occurring under standard conditions. Such precautions are not essential for the present compositions.

Further, D2 does not address in any manner, the concept of solubilizing the drug and then incorporating it in a gastroretentive matrix to improve drug bioavailability which has been disclosed by the applicants of the present invention. The applicants respectfully submit that the present invention specifically provides gastroretentive compositions of at least one active pharmaceutical ingredient of low bioavailability, which could be due to low aqueous solubility and/or limited absorption in the gastrointestinal tract, wherein the solubility of the drug is increased prior to its incorporation in a gastroretentive matrix and controlling its release. The present invention is thus particularly useful for drugs having a narrow therapeutic window of absorption wherein the combination of gastro-retention and solubilization allows a continuous trickling of solubilized drug thereby maximizing its bioavailability.

The present application as filed on p.9, line 25, specifically states "In a first illustrative embodiment, a controlled release, gastro-retentive swelling system incorporating solubilized drug is contemplated". Thus since D2 does not involve the concept of solubilization, it is very different from the present invention.

Against this background, Applicants have amended claim 27, to overcome the anticipation rejection by the examiner.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the cited reference neither teaches nor suggests the presently claimed compositions, and withdrawal of this rejection is earnestly solicited.

Rejection of Claims Under 35 U.S.C. § 103(a)

The Examiner rejected claims 2-31 under 35 U.S.C 103(a) as obvious over Singh et al., Doshi et al. and Flashner-Barak et al, US 6,881,420.

The shortcomings of the Singh et al. and Doshi et al. references were discussed above with respect to the anticipation rejections. For the same reasons discussed above, these two references in combination, with or without the third reference, neither teach nor suggest the presently claimed invention.

Singh et al (WO2001/022791A2) being referred to as D1, provides controlled release formulations of nimesulide for once-a-day administration with reproducible bioavailability.

Though D1 provides that nimesulide may be combined with other suitable long-acting drugs for synergistic activity, wherein the other drug may be present in non-controlled release form like salbutamol; it does not teach development of controlled release formulations of salbutamol. On contrary, the applicants of the present invention disclose controlled release gastro-retentive compositions of one or more pharmacologically active agents showing low bioavailability such as salbutamol amongst others. Thus, D1 does not in any manner imply the development of controlled release composition of salbutamol, thereby suggesting that it cannot be obvious to choose salbutamol, amongst the list of other pharmaceutically active ingredients for the development of controlled release formulation of the present invention.

Further, D1 does not relate to gastroretentive compositions and does not teach that the synergistic use of a biocompatible swelling agent and a swelling enhancer would lead to any gastroretention of the dosage form. D1 also does not specifically disclose any prior integral requirement of solubilization of nimesulide before its incorporation in the controlled release formulations. But D1 instead needs the use of nimesulide in the micronized form to give compositions with reproducible bioavailability.

Flashner – Barak et al (US 6881420 B2), hereinafter referred to as D3, discloses compositions and dosage forms for delivery of anti-neoplastic drugs such as irinotecan that are (a) amenable to absorption through the stomach, jejunum or duodenum and (b) which have poor oral bioavailiability attributable to either P-glycoprotein efflux pump or to pre-systemic deactivation, through parts of the gastrointestinal tract that have less activity for detrimental pre-systemic metabolism or less activity of the P-glycoprotein efflux pump. D3 utilizes hydrogels along with superdisintegrants and tannic acid to develop their formulations.

Thus the field of invention of D3 does not present any need of solubilizing the active agent prior to its incorporation into the gastroretentive dosage but the field relates to enhancing the bioavailability of anti-neoplastic drugs that have poor oral bioavailability due to either P-glycoprotein efflux pump or to pre-systemic deactivation by addressing these specific issues. Hence a teaching of solubilization cannot be contemplated via D3. Further, it is a common practice to include in pharmaceutical formulations, lubricants, as used in D3 to reduce adhesion and ease release of the product from the dye like polyethylene glycol, hydrogenated castor oil, hydrogenated vegetable oil, where they are generally employed at levels lower than that required for their use as solubilizers. Moreover, in context of D3 these lubricants do not find any reason to

be correlated to solubilizers, since the object of the invention has not been directed at all to solubilization of the drug before gastroretention. Further, the surfactants based on vegetable oils used in the present invention are transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oil, and hydrogenated vegetable oils like PEG-40 hydrogenated castor oil, unlike utilization of hydrogenated castor oil or hydrogenated vegetable oil as in D3.

Thus, since the object of D3 and any of the teachings of D3 do not relate to solubilization, it is not possible to draw any motivation from D3 or even from D3 in combination with D1 to employ solubilized version of the drug to develop controlled released gastroretentive pharmaceutical formulations of the present invention.

Further, Doshi et al (US 7157100 B2, prior publication as US 2003/0232081), being referred to herein as D2, as discussed previously, provides a floating bilayer gastro-retentive system, wherein the first layer provides for immediate drug release and the second layer swells and gels in the presence of fluid of the gastric environment resulting in volume expansion and entrapping of the gas generated by reaction of gas generating component and the fluid of the environment. D2 does not disclose any requirement for solubilization of the drug prior to incorporation into the gastroretentive compositions for enhancing the bioavailability. Thus neither D2 nor combination of D2 with D1 and/or D3 provides any motivation towards attempting to solubilize the low bioavailable drug prior to synergistically combining it with gastroretention.

Moreover, even if an attempt is made to combine the teachings of the D1, D2 and/or D3, any person of ordinary skill in the art will not be able to arrive at compositions of the present invention, since solubilization of the active, especially prior to incorporation in gastroretentive matrices is not taught by any of them, either individually or collectively. Though D1 discloses controlled release formulations and D2 and D3 disclose gastroretentive compositions, none of them teach solubilization of the active to increase its bioavailability prior to its incorporation in a gastroretentive matrix and controlling its release, taught by the instant invention. Further combined teachings of D1, D2 and D3, do not motivate solubilization of the drug and its synergistic combination with gastroretention as disclosed in the present invention.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the cited reference neither teaches nor suggests the presently claimed compositions, and withdrawal of this rejection is earnestly solicited.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Please charge any additional fees or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

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